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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/207,188	12/08/98	BLAKE M	2016-4005US1

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MORGAN & FINNEGAN
345 PARK AVENUE
NEW YORK NY 10154

EXAMINER	
DEVI,S	
ART UNIT	**PAPER NUMBER**
1645	14

DATE MAILED: 06/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/207,188	Blake et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *11/17/00.*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *61-79* is/are pending in the application.

4a) Of the above, claim(s) *73-79* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *61-72* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Previous Office Action Vacated

1) The previous non-final Office action mailed 02/12/01 is hereby vacated and is replaced with the instant Office Action.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/17/00 (paper no. 11), which amendment has been entered.

Status of Claims

3) Claims 61-79 are pending in this application.

Claims 73-79 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 61-72 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 9(a) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the specification.

7) The objection to the description for Figure 4 made in paragraph 9(b) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the specification.

8) The objection to the specification made in paragraph 9(c) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the specification.

9) The objection to the specification made in paragraph 9(d) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' clarification.

10) The objection to claim 61 made in in paragraph 16(a) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the claim.

11) The objection to claim 70 made in in paragraph 16(b) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn partly in light of the Applicants' explanation.

Applicants state that the term "QS21" is definite. The Office would like to clarify that claim 70 was not rejected as being "indefinite", instead the claim was objected to.

Objection(s) Maintained

12) The objection to the description for Figure 1 made in paragraph 9(b) of the Office Action mailed 07/14/00 (paper no. 7) is maintained for reasons set forth therein. Applicants have not addressed the issue.

Rejection(s) Withdrawn

13) The rejection of claim 61 made in paragraph 11(a) of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn.

14) The rejection of claim 62 made in paragraph 11(b) of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C 35 § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

15) The rejection of claim 63 made in paragraph 11(c) of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C 35 § 112, second paragraph, as being indefinite, is withdrawn upon further consideration.

16) The rejection of claim 67 made in paragraph 11(d) of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C 35 § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

17) The rejection of claim 68 made in paragraph 11(e) of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C 35 § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

Rejection(s) Maintained

18) The rejection of claims 61-63, 68 and 69 made in paragraph 13 of the Office Action mailed 07/14/00 (paper no. 7) under 35 U.S.C § 102(b) as being anticipated by Reimer *et al.* (*Carbohydr.*

Res. 232: 131-142, 1992), is maintained for reasons set forth therein and herebelow.

Applicants argue that Reimer's method does not use a group A streptococcal polysaccharide comprising about 3 to about 30 repeat units. The Applicants' argument has been carefully considered, but is not persuasive.

Instant claims are directed to a method of immunizing a mammal comprising administering an immunogenic amount of the recited polysaccharide of formula (I) covalently linked to a protein, wherein n in the formula encompasses a number of "about 3". The claimed method is not required to induce protection. The specification does not provide a definition describing what is encompassed in the recitation "about 3". The recitation in the base claim, "about 3", is interpreted as being equivalent to 3 ± 1, $3\pm>1.5$ or 3 ± 2, and therefore, Reimer's method anticipates the instant invention.

The immunization method of Reimer *et al.* is described in paragraph 13 of the Office Action mailed 07/14/00. Reimer's method of immunizing a mammal comprising administering a group A streptococcal polysaccharide conjugated to a protein anticipates the instantly claimed method, because Reimer's conjugate comprises a group A polysaccharide of the recited formula wherein n is equivalent to one or more than one trisaccharide unit (i.e., "about" 3). For example, see the conjugates 1a, 2a and 3a as depicted on page 136, below Table 1. The Reimer's conjugate(s) is contained in PBS and Freund's complete adjuvant and the conjugate is used for immunization of rabbits (see page 133, first full paragraph). Reimer *et al.* also teach the synthesis and conjugation to a protein of two trisaccharide sequences (i.e., n=2) (see the paragraph bridging 140 and 141, and the formula on page 141). The rejection stands.

19) The rejection of claims 61-72 made in paragraph 15 of the Office Action mailed 07/14/00 (paper no. 7) 35 U.S.C § 103(a) as being unpatentable over Reimer *et al.* (*Carbohydr. Res.* 232: 131-142, 1992) in view of Jennings *et al.* (US 4,356,170) and Barnes *et al.* (WO 87/06590), is maintained for reasons set forth therein and those set forth below. In this rejection, the recitation in the base claim, "about 3", is interpreted as being equivalent to 3+1, 3+>1.5, 3+2.

Applicants contend that, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation either in the references or "in the knowledge generally available to one of ordinary skill in the art to modify the reference", a reasonable expectation of success or reference(s)

teaching or suggesting all the claim limitations. Applicants allege that the Office has not provided evidence of motivation or suggestion to modify the references and has failed to show a reasonable expectation of success. Applicants further point to the McCarty Declaration, filed 12/08/99, stating that the art did not consider the group A streptococcal polysaccharide to be relevant in connection with "eliciting a protective immunogenic response". Applicants also point to the issuance of the US patent 5,866,135 directed to the product used in the instant invention.

The Applicants' arguments have been carefully considered, but are not persuasive. Applicants are reminded that the instant claims are drawn to a method of "immunizing a mammal" as opposed to a method of "eliciting a protective immune response in a mammal". The Office agrees with the Applicants that there must be motivation in the references or "in the knowledge generally available to one of ordinary skill in the art" to modify the reference to establish a *prima facie* case of obviousness. In the instant rejection, the motivation comes from the knowledge generally known to those skilled in the art of conjugate vaccines that a microbial protein, such as tetanus toxoid or diphtheria toxoid, would serve as a clinically more useful carrier protein in a conjugate compared to BSA. One would have had a reasonable expectation of success in substituting Reimer's BSA with Jennings' medically useful carrier protein, such as diphtheria toxoid or tetanus toxoid, to produce the instant invention since such a substitution has been conventionally practiced in the art of conjugate vaccines with success. Absent a showing that substituting Reimer's BSA with Jennings' tetanus toxoid or diphtheria toxoid would result in a streptococcal polysaccharide-protein conjugate that is non-immunogenic or not optimally immunogenic, the rejection stands. As set forth in paragraph 15 of the Office Action mailed 07/14/00 (paper no. 7), the motivation to substitute Reimer's Freund's complete adjuvant with Jennings' non-toxic adjuvant, such as, aluminum hydroxide or aluminum phosphate, comes from the teachings of Barnes *et al.* who explicitly teach that Freund's complete adjuvant is unsatisfactory for human use since it causes large undesired lesions at the site of injection. The rejection stands.

With regard to Applicants' remarks on the McCarty's statement about the protective immunogenic response, Applicants are reminded that instant methods are drawn to a "method of immunizing a mammal" with the recited conjugate, which is clearly taught by Reimer *et al.* With regard to Applicants' remarks on the issuance of the US patent 5,866,135, it should be noted that

the prosecution of one application does not have to duplicate that of a previous application. Each case is individually reviewed and prosecuted on its own merits.

Rejection(s) under 35 U.S.C § 103(a)

20) Claims 61-63, 68 and 69 are rejected under 35 U.S.C § 103(a) as being unpatentable over Reimer *et al.* (*Carbohydr. Res.* 232: 131-142, 1992).

In this rejection, the recitation in the base claim, "n is a number from about 3", is interpreted as 3. The teachings of Reimer *et al.* have been described in paragraph 13 of the Office Action mailed 07/14/00 and further discussed in paragraph 18 above. Although Reimer *et al.* do not expressly teach a method of immunizing a mammal comprising administering a group A streptococcal polysaccharide of the formula recited in claim 61 wherein n is 3 to about 30 and the polysaccharide is conjugated to a protein wherein, Reimer *et al.* explicitly suggest the use of glycoconjugates prepared from oligosaccharides that span "two or more branch points" (see page 142). It is also noted that the structure of the Group A streptococcal oligosaccharide conjugates on pages 135 and 136 of Reimer *et al.* depict $[.....]_n$. One skilled in the art at once would envisage $[.....]_n$ to be equivalent to n =1, 2, 3, 4, 5, 6 etc., in the conjugate (otherwise the depiction of $[.....]_n$ is meaningless). Reimer *et al.* further teach that oligosaccharides of increasing complexity exhibited increasing potency. Reimer *et al.* also provide data that "suggest that both the size and branch point are essential features of the Group A epitope" (see page 141, third full paragraph). Reimer *et al.* teach the branch point of the streptococcal Group A antigen to be the crucial element of the epitope recognized by antibodies that are able to bind the native antigen (see paragraph bridging 141 and 142).

Given the teachings of Reimer *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to increase the number of branched trisaccharide unit(s) in the conjugate used in the method of immunization of Reimer *et al.* from 1 or 2 to more than two, (for example, 3 or 4 or 10 etc.,) to produce the instant invention, with a reasonable expectation of success, because Reimer *et al.* expressly suggest the preparation and use of glycoconjugates prepared from Group A streptococcal oligosaccharides having "two or more branch points" and the significance of having such branch points in the oligosaccharide as these

branch points serve as crucial elements of the epitope recognized by antibodies reactive with the native Group A strpetococcal polysaccharide. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of producing a method of immunization that uses a more complex oligosaccharide comprising more than two branch points, since such oligosaccharides are taught by Reimer *et al.* to exhibit increased potency and since a skilled artisan would understand that glycoconjugates of increased potency are ideally desired in the art of vaccines or antimicrobial immunization.

Claims 61-63, 68 and 69 are *prima facie* obvious over the prior art of record.

21) Claims 61-72 are rejected under 35 U.S.C § 103(a) as being unpatentable over Reimer *et al.* (*Carbohydr. Res.* 232: 131-142, 1992) in view of Jennings *et al.* (US 4,356,170) and Barnes *et al.* (WO 87/06590).

The recitation in the base claim, "about 3", is interpreted as being equivalent to 3.

The teachings of Reimer *et al.*, as modified, are described above in paragraph 20, which do not disclose the use of a bacterial protein, such as, tetanus toxoid or diphtheria toxoid, in the Group A streptococcal conjugate used in their method of immunization, the use of an adjuvant selected from the group of adjuvants recited in claim 70 and immunizing a human or human child with the conjugate.

However, protein carriers, such as, tetanus toxoid and diphtheria toxoid, for the preparation of potent conjugates and adjuvants, such as, aluminum and aluminum phosphate are conventinally used in the art of conjugate vaccines. For example, Jennings *et al.* teach the use of carbohydrates from beta-hemolytic Group A streptococci for the purpose of conjugation to a protein carrier, such as, tetanus toxoid and diphtheria toxoid (see column 3, lines 15-22 and 45-55). The polysaccharide is coupled to the protein via a free amino group (see column 3, last paragraph). The use of conjugate vaccines in human infants and the use of adjuvants including aluminum hydroxide, aluminum sulfate, aluminum phosphate or an alum is specifically disclosed (see column 4). The molecular weight of the polysaccharide disclosed is 10,000 (i.e., 10 Kd) (see column 4, lines 50-60), or can be within 2000-100,000 (see column 4, lines 21 and 22). The immunization protocol is disclosed in columns 6 and 7. The dosage ranges from 5 to 25 micrograms (see column 4, lines 40-

44).

Barnes *et al.* disclose the disadvantages of using Freund's complete adjuvant (FCA) for *in vivo* use. Barnes *et al.* teach that, when used with an antigen in an injectable form, the adjuvant often forms large lesions at the site of injection, which render the adjuvant unsatisfactory for use in humans, pets and in meat animals (see page 1, fourth full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the BSA protein carrier in the modified Reimer's Group A streptococcal oligosaccharide-protein conjugate that is used in Reimer's method of immunization of a mammal, with Jennings' medically useful protein carrier, such as, tetanus toxoid or diphtheria toxoid, and substitute Reimer's FCA adjuvant with Jennings' aluminum hydroxide or aluminum phosphate, to produce the instant invention, with a reasonable expectation of success. One skilled in the art would have been motivated to make the substitution for the expected benefit of having a clinically more useful microbial protein carrier than BSA in the conjugate and a clinically acceptable, non-toxic adjuvant for use in Reimer's method of immunization, since Barnes *et al.* teach that Freund's complete adjuvant is unsatisfactory for human use, because it causes large lesions at the site of injection. Absent a showing that substituting Reimer's BSA with Jennings' tetanus toxoid or diphtheria toxoid in Reimer's conjugate would result in a streptococcal polysaccharide-protein conjugate that is non-immunogenic or not optimally immunogenic, claims 61-72 are *prima facie* obvious over the prior art of record.

Double Patenting Rejection(s)

22) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to

overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

Claims 61-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the instantly claimed method of immunization is encompassed in the scope of claims 26-33 of the U.S. Patent 5,866,135.

Furthermore, there is no apparent reason why Applicants were prevented from presenting claims corresponding to those of the instant application during the prosecution of the parent application which matured into US Patent 5,866,135. See *In re Sachneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Remarks

23) Claims 61-72 stand rejected.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which receives papers seven days a week and 24 hours a day.

25) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Furthermore, there is no apparent reason why Applicants were prevented from presenting claims corresponding to those of the instant application during the prosecution of the parent application which matured into US Patent 5,866,135. See *In re Sachneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

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S. Devi, Ph.D.
Patent Examiner
June 2001

Jasemine C. Chambers

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600